Code 4160
Q1 Charge and Questions

Food Advisory Committee Meeting
July 13-15, 2005
Approaches to Establish Thresholds for Major Food Allergens and for Gluten in Food

Charge

The Food Advisory Committee is being asked to evaluate the Threshold Working Group draft report "Approaches to Establish Thresholds for Major Food Allergens and for Gluten in Food." The Committee should advise the FDA whether the draft report is scientifically sound in its analyses and approaches and whether the draft report adequately considers available relevant data on major food allergens and on gluten. In addressing these issues, FDA requests that the Committee consider the following specific questions:

General

1. In addition to the four approaches identified by FDA for establishing thresholds (i.e., analytical methods-based, safety assessment-based, risk assessment-based and statutorily-derived) are there other approaches that FDA should consider? If so, please describe and explain why FDA should consider them.
2. Are FDA's criteria for selecting and evaluating the available data appropriate? If not, should any of the criteria be modified or deleted? Please describe any changes you would like to see and why. Are there additional criteria FDA should consider?
3. Recognizing that some of the key studies (i.e., challenge studies) are ongoing, what if any use of preliminary data that have not been peer-reviewed for establishing thresholds is appropriate?

Food Allergens

1. Are there distinct subpopulations of highly sensitive individuals within the allergic population for <u>each</u> of the major food allergens[1]? If so, for the safety-assessment based approach, are the proposed uncertainty factors for intraspecies differences (10-fold) and severity of response for the sensitive population (10-fold) sufficient to ensure that exposure levels will be below the level of sensitivity for the highly sensitive subpopulations? If these uncertainty factors (total of 100-fold) are not sufficient, what uncertainty factors should be used for the safety assessment-based approach?

2. Is the initial objective response seen in a clinical challenge study always an adverse effect that poses risk to human health? Is it scientifically sound to use this response to determine a LOAEL

[1] The Food Allergen Labeling and Consumer Protection Act of 2004 (P.L. 108-282) defines a "major food allergen" as one of the following eight foods or food groups or a protein derived from them: milk, egg, fish, crustacean shellfish, tree nuts, peanuts, wheat, and soybeans.

in the absence of a NOAEL? For the safety assessment-based approach, is the proposed uncertainty factor of 10-fold sufficient and appropriate to use in the absence of a NOAEL? If a clinical challenge study reports a subjective response at a lower dose than the dose that caused an objective response, should that observation be taken into account when determining the appropriate uncertainty factor?

3. In the absence of specific data that would allow thresholds to be established for each of the major food allergens, is it scientifically sound to use the threshold established for a single food allergen (e.g., peanuts) as the threshold for all major food allergens? If so, which food or foods could serve this function? If not, is there a more appropriate method to use?

4. The draft report discusses the available data on the levels of protein present in highly refined oils (e.g., oil that is hot solvent extracted, refined, bleached, and deodorized). Is there any physiological reason (e.g., food matrix effect, denaturation of protein) why the protein levels in highly refined oils could not be used as the basis for establishing a threshold for other allergenic foods? Are there any other limitations that should be considered in applying this approach to the eight allergenic foods?

Gluten and Celiac Disease

1. Is there a distinct subpopulation of individuals with celiac disease that have an increased sensitivity to gluten? If so, for the safety-assessment based approach, is the proposed uncertainty factor for intraspecies differences (10-fold) sufficient to ensure that exposure levels will be below the level of sensitivity for this highly sensitive subpopulation? If this uncertainty factor (10-fold) is not sufficient, what uncertainty factors should be used?

2. Is it scientifically sound to use data from short-term clinical studies that evaluate the effects of acute gluten exposure to predict the effects of long-term gluten exposure in gluten sensitive individuals? What uncertainty factor is appropriate for thresholds developed using available short-term clinical studies in order to prevent adverse events associated with chronic effects?

3. Are current data sufficient to conclude that a portion of celiac disease patients are (or are not) also susceptible to gluten proteins naturally occurring in oats (i.e., prolamins and glutelins)? If not, what additional data is needed to draw such a conclusion?

4. Are all individuals with celiac disease equally at risk for developing consequences (e.g., cancer) and increased mortality from the long-term ingestion of gluten? Are current data from clinical studies or from individuals with celiac disease on a gluten-restricted diet sufficient to estimate the magnitude of any increased risk of mortality for these individuals?

5. Is evidence of minimal intestinal pathological change (e.g., increased intraepithelial lymphocytes) following a gluten challenge, an appropriate symptom upon which to base a LOAEL for long-term consequences? Are other biomarkers, such as clinical symptoms or more severe intestinal pathological changes, more accurate predictors of long-term consequences?